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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
ALSTRUM ACEVEDO, JAMES HENRY	
ART UNIT	**PAPER NUMBER**
1616	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/582,473	OKPALA, JOSEPH	
	Examiner	Art Unit	
	JAMES H. ALSTRUM ACEVEDO	1616	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *36-66* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *36-66* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *12 June 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *2/6/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 36-66 are pending. Applicant cancelled claims 1-35 in a preliminary amendment submitted on July 6, 2006.

Priority

Receipt is acknowledged of papers submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file.

Specification

The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 37 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 37 is vague and indefinite, because the metes and bounds of the phrase "any other device capable of simulating at least one drug delivery target region..." is ambiguous. Thus, an

ordinary skilled artisan would have to guess as to the metes and bounds of the references "any other device…"

Claim Rejections - 35 USC § 102

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 36-44, 47-57, 62-66 are rejected under 35 U.S.C. 102(b) as being anticipated by Leith (U.S. Patent No. 5,304,125) (IDS reference).

Applicant claims a method of producing particles from a feedstock material comprising (i) providing a mimicked respiratory system, (b) providing an engineering medium, (c) operating the mimicked respiratory system to simulate a controlled inhalation flow rate, (d) providing an aerosolized feedstock material within the mimicked respiratory system, and (e) collecting the resultant engineered particles from a simulated drug delivery system.

Claim Interpretation

The term filtered is broadly interpreted to mean an item that removes something from whatever is passed through it. Aerosolization from an aerosol generator (e.g. a metered dose inhaler or SPINHALER®) is interpreted as meaning spraying into the mimicked respiratory system.

In one embodiment of Example 2 Leith discloses providing a composition comprising (i) **lactose (i.e. a disaccharide; an excipient)** that has been sieved through a 400 mesh sieve to ensure a particle size of no greater than 37 microns (i.e. pre-treated and filtered) and (ii) **amiloride (i.e. a therapeutic active agent)**, wherein the mixture of (i) and (ii) **is re-sieved**

through a 400 mesh sieve (i.e. pre-treated) (col. 8, lines 18-45). The mixture is placed into a gel capsule, which is inserted into a SPINHALER®. **Air** at **60 L/min (Lpm) flowed through** the aerosol generator (i.e. SPINHALER®), impactor (described in connection with Figures 1-4), **a glass "throat", and a plastic "distal pharynx**" (col. 8, lines 29-34). Within the distal pharynx an isokinetic sample at a 28.3 Lpm flowed through a nozzle and **into an Andersen impactor**, wherein the remaining 31.7 Lpm was drawn off through a bypass line **that led to a filter**, rotameter, and **to a vacuum** (col. 8, lines 34-39). To conduct a test, **vacuum was applied simultaneously to both the Andersen impactor and the bypass lines, and air flow at 60 Lpm was maintained for four seconds to simulate an inspiration**; six inspirations were used for each capsule (col. 8, lines 41-45). After each experiment, the apparatus was disassembled and each component washed individually to remove amiloride and lactose particles. **Washes from each component were analyzed for amiloride**; this data was used to calculate concentrations of amiloride at each sample and determine (i) the mass of amiloride in each test left in the capsule, (ii) the amount caught in the impactor, **the "oropharyngeal dose**" (i.e. mass caught in throat and distal pharynx and Andersen impactor stages for particles larger than 4.7 microns) and (iii) the respirable dose (i.e. mass caught in Andersen stages for particles smaller than 4.7 microns) (col. 9, lines 13-47).

In an alternative embodiment (col. 8, line 46 through col. 9, line 13), **amiloride used with a metered dose inhaler (MDI) is milled until essentially all particles are smaller than 2.6 microns** (i.e. pre-treatment). Amiloride is **packaged in an MDI with freon propellants (i.e. trichlorofluoromethane and dichlorodifluoromethane; pressurized liquids) and a surfactant (sorbitan trioleate; i.e. an excipient)** (i.e. pre-treatment with a liquid). **A spacer is**

attached to the MDI to allow evaporation of propellant and remove **larger particles by sedimentation** (i.e. filter before the mimicked respiratory system; provides a local environment distinct from the remainder of the mimicked respiratory system). It is the Examiner's position that the spacer used by Leith must consist of at least one inlet and at least one outlet, because if it did not the aerosolized formulation from the MDI could not pass into the mimicked respiratory system (e.g. Andersen cascade impactor). **Prior to each release of drug** from the MDI, the canister was **shaken vigorously** (i.e. agitation). Similar to the SPINHALER®, vacuum is applied, and an air flow of 60 Lpm is used, wherein 28.3 Lpm is diverted to the Andersen impactor and 1.7 Lpm through the bypass line. Similarly to the tests with the SPINHALER® the apparatus is disassembled and the amiloride in the different parts of the apparatus is quantified (col. 9, lines 13-47).

Regarding the temperature during the experiments, Leith is silent. However, because Leith does not state that the temperature in the apparatus is increased by heating or decreased by cooling, it is concluded that the temperature is about standard room temperature (i.e. about 25°C).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Applicant Claims
2. Determining the scope and contents of the prior art.
3. Ascertaining the differences between the prior art and the claims at issue, and resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 36-66 are rejected under 35 U.S.C. 103(a) as being unpatentable over Leith (U.S. Patent No. 5,304,125) (IDS reference), Cripps et al. (US 2003/0180228), and Forman et al. (U.S. Patent No. 5,948,439), as evidenced by Radhakrishnan et al. (U.S. Patent No. 5,192,528).

Applicant Claims

Applicant claims a method as described above wherein (i) in some embodiments the feedstock formulation comprises a therapeutic agent selected from a group including salmeterol xinafoate, (ii) in some embodiments the temperature of the mimicked respiratory system is between 34 °C and 42 °C, (iii) in some embodiments the feedstock material contains at least one effervescent substance that may evolve carbon dioxide upon combination of a base and an acid.

Determination of the Scope and Content of the Prior Art (MPEP §2141.01)

The teachings of Leith are set forth above. Leith's teachings establish that procedures were known in the art to evaluate aerosolized solids and/or liquid formulations to ascertain the

delivery of therapeutic agents to different parts of the respiratory system based on a mimicked respiratory system.

Cripps teaches **HFA aerosol formulations of salmeterol xinafoate** (i.e. metered dose inhaler [MDI] formulations) and evaluates the aerodynamic properties of said formulations by **aerosolization of 10 shots into an Andersen Cascade Impactor**, which is **quantitatively washed, and the amount of drug deposited thereon is quantified by HPLC analysis of the washings** [0164]-[0176]. In some embodiments, the tested MDI formulations are tested under accelerated conditions of storage at **a temperature of 40 °C and 75% RH** [0173]-[0175].

Forman teaches **effervescent granules for the release and efficient dispersion of an herbal preparation** in bathing water for topical administration **or into steam for inhalation** (title; abstract; col. 1, lines 5-10 and 23-29). The effervescent granules comprise (i) herbal extracts and/or essential oils, **(ii) sodium bicarbonate (i.e. a base), (iii) citric acid, and (iv) tartaric acid** (col. 2, lines 45-64; col. 5, lines 60-65; col. 6, line 1 through col. 10, line 19).

Radhakrishnan **correlates the different stages of the Andersen Cascade Impactor with different regions of a human's respiratory system, such as the alveoli and terminal bronchii** (Figure 1; col. 3, lines 62-66; and col. 6, lines 20-46).

Ascertainment of the Difference Between Scope the Prior Art and the Claims (MPEP §2141.012)

Leith lacks the teaching of feedstock material comprising therapeutic agents other than amiloride. This deficiency is cured by the teachings of Cripps and Forman. Leith lacks the teaching of the temperature of the mimicked respiratory system being between 34 °C and 42 °C. This deficiency is prima facie obvious and is also cured by the teachings of Cripps. Leith lacks

the teaching of a feedstock that contains at least one effervescent substance that may evolve carbon dioxide upon combination of a base and an acid. This deficiency is cured by the teachings of Forman.

Finding of Prima Facie Obviousness Rationale and Motivation (MPEP §2142-2143)

It would have been *prima facie* obvious to a person of ordinary skill at the time of the instant invention to combine the teachings of Leith, Cripps, and Forman, as evidenced by Radhakrishnan, because all references teach inhalable compositions and Leith teaches a conventional methodology of evaluating the aerodynamic properties of the inhaled formulations and ascertaining where the likely destination within a human respiratory system. An ordinary skilled artisan cognizant of the teachings of Leith and Cripps would readily appreciate that Leith's methodology could be used to evaluate the aerodynamic characteristics of Cripps' salmeterol xinafoate formulations, as evidenced by the fact that Cripps states the use of an Andersen Cascade Impactor to evaluate the invented salmeterol xinafoate HFA formulations, administered from a MDI. An ordinary skilled artisan would have been motivated to utilize different drug formulations dispensed (i.e. aerosolized) from a dry powder inhaler, such as SPINHALER®, or from a MDI with Leith's apparatus to obtain information about the aerodynamic characteristics of the drug formulations upon aerosolization from an inhaler. An ordinary skilled artisan would have had a reasonable expectation of testing other inhalable formulations with Leith's apparatus, because Leith's apparatus was designed to evaluate the aerodynamic properties of said formulations. An ordinary skilled artisan would have been similarly motivated to utilize an inhalable feedstock comprising effervescent materials and

would similarly have had a reasonable expectation of successfully ascertaining where the steam-inhaled herbal extracts and/or essential oils in Forman's invented compositions would reach in the respiratory system. The teachings of Radhakrishnan establish that the ordinary skilled artisan would recognized the different stages of the Andersen Cascade Impactor as correlating to different parts of the human respiratory system. Thus, based upon the aforementioned the ordinary skilled artisan would be able to systematically tune the aerodynamic properties of an inhalable formulation and evaluate the progress in targeting differing regions of the human respiratory system. Therefore, the claimed invention, as a whole, would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, because the combined teachings of the prior art is fairly suggestive of the claimed invention.

Conclusion

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Radhakrishnan et al. (U.S. Patent No. 5,049,389) is relevant because it similarly discloses information correlating the different stages of the Andersen Cascade Impactor to different regions of the human respiratory system. Loebenberg et al. (US 2007/0031490) is not prior art, but is considered relevant because it teaches inhalable effervescent powders comprising (i) an inorganic or organic carbonate, (ii) an acid), and in some embodiments active agents, such as antibiotics.

Claims 36-66 are rejected. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to James H. Alstrum-Acevedo whose telephone number is (571) 272-5548. The examiner can normally be reached on M-F, ~10:00-6:00 and Saturdays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Johann Richter can be reached on (571) 272-0646. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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